

Primary thyroid lymphoma: The 40 year experience of a UK lymphoma treatment centre

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Abstract. We report the 40-year unselected experience of a UK lymphoma treatment centre. Between 1970 and 2010, 3363 cases of non-Hodgkin lymphoma were managed by the Sheffield Lymphoma Team. Seventy cases of primary thyroid lymphoma were identified during this time. This retrospective review of the clinical and pathological features of patients with thyroid lymphoma comprises one of the largest series conducted in the UK. The series included 57 females and 13 males with a median age at diagnosis of 69.5. The pathological subtypes were diffuse large B-cell lymphoma (DLBCL) in 50 patients, MALT lymphoma in 13, indolent B-cell lymphoma not otherwise specified (NOS) in 6 and T cell lymphoma in one patient. Of the 64 patients fully staged, 53 had Stage IE and 11 Stage IIE disease. Management modalities included surgery, chemotherapy, radiotherapy or combination treatment. Five-year survival rates for DLBCL, MALT lymphoma and indolent B-cell lymphoma NOS were 45%, 62% and 75%, respectively, with a median overall survival of all histological subtypes of 68 months (range 0-148) or 5.7 years. The outcomes of this series confirm previous experience. If treatment is needed after surgery radiotherapy alone is sufficient for Stage I and II low grade thyroid lymphoma. Combination chemotherapy or adequate chemotherapy followed by radiotherapy is warranted in high grade thyroid lymphoma.

Introduction

Primary thyroid lymphoma is a rare disease, representing only 2-8% of all thyroid malignancies and 1-2% of all newly diagnosed extranodal lymphomas (1-5). The majority of thyroid lymphomas are B-cell lymphoma, although there have been rare cases of Hodgkin and T cell lymphoma.

The most common lymphoma of the thyroid is diffuse large B-cell lymphoma (DLBCL) accounting for 50-70% of all cases

(6). Mucosa-associated lymphoid tissue (MALT) lymphoma is a distinct lymphoma originating from parafollicular B cells, developing as a result of chronic inflammation and lymphoplasmacytic infiltration as seen in Hashimoto's thyroiditis, hence the close correlation between the two diseases. MALT lymphomas are thought to account for 25-30% of all thyroid lymphomas (6). Histological evidence of mixed MALT lymphoma and DLBCL support the theory of transformation of DLBCL from a MALT lymphoma. This mixed subtype appears to have the same clinical behaviour as DLBCL (6). Primary thyroid lymphoma is often diagnosed and managed as two distinct clinical entities. High grade lymphomas with a more aggressive clinical course include DLBCL and T cell lymphoma, whereas MALT and follicular lymphomas are considered low grade with a more indolent natural history. Differentiation between the two clinical entities is important as it determines appropriate treatment options.

As with Hashimoto's disease, thyroid lymphomas occur more commonly in females than in males with a ratio of 2:1, though in some series this has been reported to be as high as 14:1 (7).

Patients usually present with an enlarging neck mass, more rapidly growing in DLBCL than MALT lymphoma, often causing local obstructive symptoms and sometimes associated with cervical lymphadenopathy. Patients are often euthyroid although hypothyroidism can be seen in up to 10% of cases (6,8).

Diagnosis is usually achieved by ultrasound guided needle biopsy of the thyroid lesion although open biopsy provides further architectural detail confirming the diagnosis. Accurate staging is important in determining therapeutic options and predicting prognosis. Staging of disease beyond the neck with imaging of the chest, abdomen and pelvis and bone marrow examination is essential to establish optimal therapy for the disease. Primary thyroid lymphoma is staged according to the Ann Arbor staging classification, with up to 90% of patients presenting with early stage disease. Stage IE (extranodal) is defined as lymphoma confined to the thyroid gland. Stage IIE denotes spread beyond the thyroid to regional lymph nodes (6,9).

The overall 5 year survival for stage IE and IIE primary thyroid lymphoma is 80% and 50% respectively, compared with less than 35% for Stage IVE (6,7).

Traditionally the mainstay of treatment of thyroid lymphoma was surgery followed by radiotherapy if resection was incomplete. Unfortunately this led to significant relapse rates. So multimodality treatment with combination chemotherapy and

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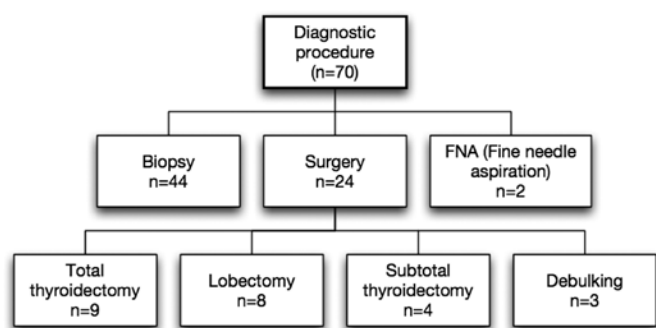


Figure 1. Patients undergoing different diagnostic procedures.

radiotherapy is now becoming standard practice, in particular for DLBCL. Treatment of MALT lymphoma is varied, with stage IE and IIE disease responding well to local therapy such as surgery or radiotherapy alone (10,11).

The aim of this retrospective analysis is to describe the clinical and pathological features and survival of a series of consecutive patients with primary thyroid lymphoma managed by the Sheffield Lymphoma Team over a forty-year period from 1970 to 2010. To our knowledge this study is one of very few non-selective series, examining a significant number of thyroid lymphoma cases accrued over four decades.

Materials and methods

The lymphoma database at Weston Park Hospital, Sheffield, was used to identify all patients diagnosed with thyroid lymphoma treated by the Sheffield Lymphoma Team between 1970 and 2010. In total 3363 cases of non-Hodgkin lymphoma (NHL) were recorded over the period of the study. The database identified a potential of 83 patients with NHL of the thyroid. Of these, notes were retrieved on 78 patients. Three patients were excluded as they had Stage IV disease and it was uncertain if the thyroid disease was truly primary. Two further patients were excluded as they were found, respectively, to have plasmacytoma and anaplastic carcinoma of the thyroid gland, and three others because pathology was not confirmative. Thus, in total, 70 patients were included in this retrospective analysis (Table I).

Case notes, pathology records and the chemotherapy electronic prescribing database were accessed to obtain the following information: patient demographic details, presenting features, stage of disease, histological subtype, treatment and survival.

Pathology reports were reviewed individually by a consultant haemato-pathologist (JRG).

Overall survival was calculated from time of diagnosis until death or date the patient was last seen using Kaplan-Meier survival graphs.

Results

Clinical features. Of the 70 patients, 57 were female and 13 male (female: male ratio of 4.4:1). The mean age at presentation was 66 years with a range of 20 to 90. All of the patients in the study were white British.

The most common presenting feature was a swelling or mass in the neck (97%), followed by dysphagia (16%). Biochemical derangements (hypercalcaemia and thyrotoxicosis) were seen in one patient. A total of 13 patients presented with stridor, 9 (70%) of whom required an urgent tracheostomy. Only 4 had 'B' symptoms (weight loss, night sweats, pyrexia) at presentation.

The majority of patients (91%) were fully staged. Poor performance status was the main reason for incomplete staging investigations.

Stage. Of the 64 patients fully staged, 51 had Stage IEA and 9 Stage IIEA. Two patients each had Stage IEB and Stage IIEB disease.

Histology. Histopathological diagnosis was made by biopsy of the thyroid gland in 44 patients and by fine needle aspiration (FNA) in two. The remaining patients underwent, in decreasing frequency total thyroidectomy, lobectomy, subtotal thyroidectomy or debulking surgery (Fig. 1).

Non-Hodgkin Lymphoma was sub-typed in accordance with the WHO 2008 classification (12). Indolent lymphomas (27% of total) were mostly MALT lymphoma, with the remaining follicular or unclassifiable tumours grouped as indolent B-cell lymphoma not otherwise specified (NOS). Aggressive lymphomas were nearly all diffuse large B-cell lymphoma (71% of total) with only one case of peripheral T-cell lymphoma.

Treatment. Treatment of thyroid lymphoma varied in our cohort of patients and depended on histology, patient co-morbidities and performance status. Management included - no additional treatment (following surgery), radiotherapy alone, chemotherapy alone and combination treatment with chemotherapy and radiotherapy (Fig. 2).

No further treatment. Four patients did not have any additional treatment following diagnosis. Two patients, both with MALT lymphoma, achieved a complete response with total thyroidectomy. One patient aged ninety with DLBCL was too unwell for

Table I. Distribution of thyroid NHL according to histological subtypes and stage.

Histological subtype/Stage	IEA	IIEA	IEB	IIEB	Not fully staged	Total
MALT lymphoma	12	0	0	0	1	13
Indolent B-cell NOS	4	1	0	0	1	6
DLBCL	34	8	2	2	4	50
T Cell	1	0	0	0	0	1

Table II. Radiotherapy doses used in patients treated with radiotherapy alone.

Lymphoma	Radiation dose (n= no. of patients)					
	≤20 Gy	24 Gy	30 Gy	35 Gy	40 Gy	45 Gy
DLBCL	2	0	4	6	3	0
MALT lymphoma	0	1	3	0	4	1
NOS	0	0	1	2	1	1

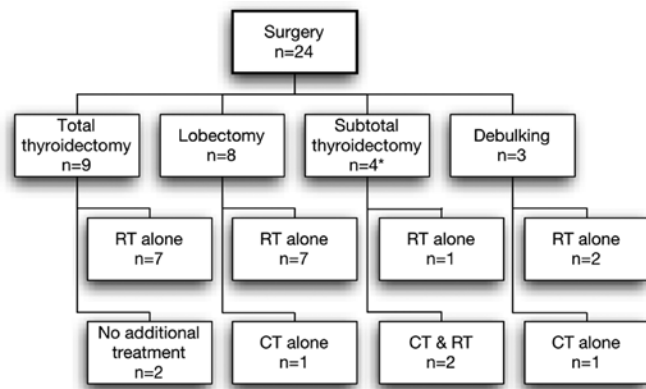


Figure 2. Patients undergoing treatment following surgery. RT, radiotherapy; CT, chemotherapy. * One patient was too unwell for further treatment.

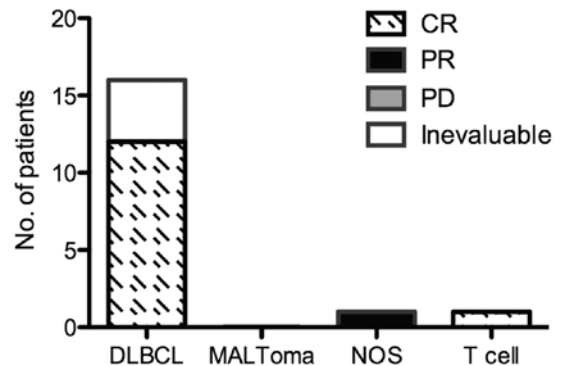


Figure 4. Outcomes of patients undergoing treatment with chemotherapy alone.

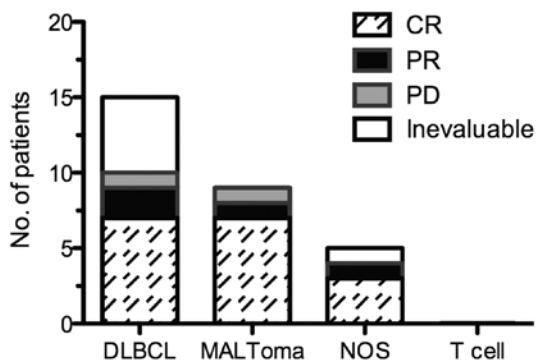


Figure 3. Outcomes of patients undergoing treatment with radiotherapy alone.

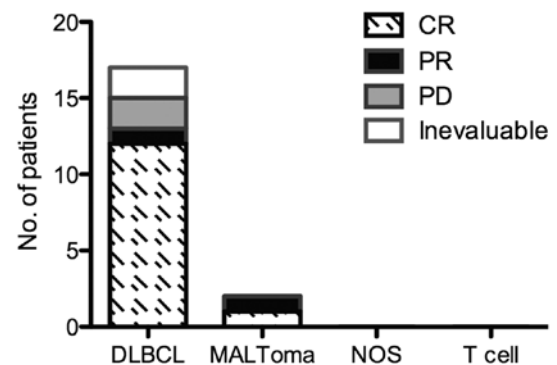


Figure 5. Outcomes of patients undergoing treatment with combination of chemotherapy and radiotherapy.

further treatment and a further patient declined chemotherapy or radiotherapy.

Treatment following surgery

Radiotherapy only. Twenty-nine (41.4%) patients were treated with radiotherapy (RT) as a sole modality (Fig. 3). This was delivered using an anterior and posterior parallel opposed pair of 6 to 8 megavoltage photons to the bilateral cervical region and the upper mediastinum to include retrosternal disease extension. Doses ranged considerably from 12.5 Gy to 45 Gy in different fractionation regimens. The most commonly used prescription was 35 Gy in 20 fractions and 40 Gy in 20 fractions (Table II).

Seventy percent of patients with MALT lymphoma compared to only 30% with DLBCL were treated with radiotherapy as

a single modality. A total of 17 patients (58.6%) achieved a complete response and 4 a partial response with RT alone.

Of the 15 DLBCL patients undergoing RT, 7 (47%) achieved CR, 2 PR and 1 patient progressed despite radiotherapy. Response was not evaluable in 5 patients as one patient failed to complete the scheduled plan due to infection, one patient died shortly after receiving radiotherapy and in three patients response was not recorded. Of the 9 patients with MALT lymphoma, 7 (78%) achieved CR, 1 patient PR and 1 PD. Two of the five patients with thyroid lymphoma NOS achieved CR with radiotherapy alone.

Chemotherapy only. Eighteen patients in total were treated with chemotherapy alone (Fig. 4). Regimens most commonly

Table III. Details of relapses in the six patients.

Age	Stage	Histology	Primary treatment	Response to primary treatment	Site of relapse	Time to relapse (months)	Second line treatment	Response to second line treatment	Survival
70	IIEA	DLBCL	RT alone	CR	Widespread disease	24	Chemo	PD	Died
69	IEA	DLBCL	3x CHOP and RT	CR	Axilla	28	Chemo	PD	Died
57	IEA	DLBCL	4x CHOP and RT	PR	Thyroid	2	Chemo	PD	Died
59	IEA	MALT	RT alone	CR	Brain	36	Chemo	PD	Died
78	IEA	MALT	3x CHOP and RT	PR	Thyroid	36	Chemo	PR	Alive

PD, progressive disease; PR, partial response; CR, complete response; CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy.

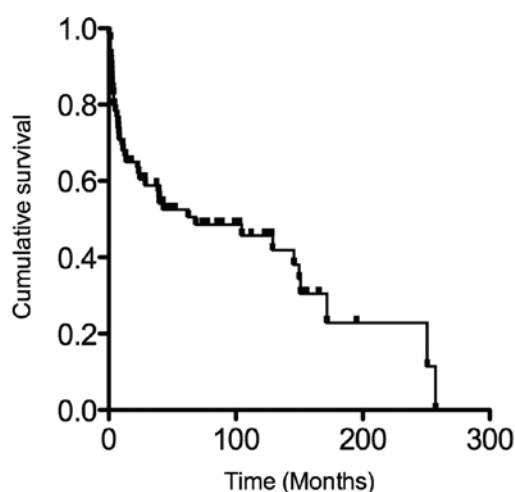


Figure 6. Overall survival for thyroid lymphoma.

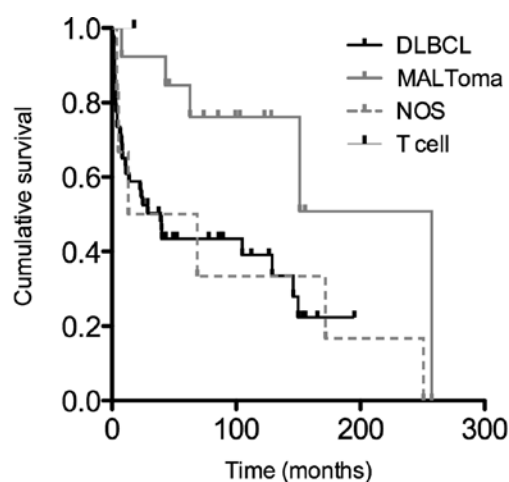


Figure 7. Overall survival for the different histopathological subtypes.

used were CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), VEDex (vincristine, epirubicin and dexamethasone), PMitCEBO (prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin and vincristine) and oral chlorambucil. The median number of cycles given was six and the mean 5.4.

The single case of thyroid T cell lymphoma was treated with 6 cycles of CHOP resulting in a complete response. Interestingly, none of the MALT lymphomas were treated with chemotherapy alone. Twelve out of the 16 patients (75%) with DLBCL treated with chemotherapy alone achieved a CR. The single case of thyroid lymphoma NOS treated with chemotherapy alone achieved a partial response to chemotherapy.

Chemotherapy and radiotherapy. Nineteen patients (27%) were treated with a combination of chemotherapy initially, followed by radiotherapy to the neck. The majority (17) were of the DLBCL subtype and only 2 had MALT lymphoma. The median number of chemotherapy cycles received was 3, although four patients received four cycles each and one patient received 8 prior to radiotherapy. CHOP chemotherapy was the most widely used regimen. Combination chemotherapy and radiotherapy

provided a complete response in 12 patients (70.5%) and a partial response in one patient with DLBCL. The majority of patients (76%) with DLBCL received a radiation dose of 40 Gy in 20 fractions, whilst three patients were treated with 30 Gy in 10-15 fractions. The two MALT lymphoma patients treated with combination chemotherapy and radiotherapy both received 40 Gy in 20 fractions (Fig. 5).

Recurrences. Of the 50 patients who responded to initial therapy, five subsequently relapsed; three of these were DLBCL and two MALT lymphoma. Only 3 patients relapsed after achieving a complete response to their initial treatment. Table III details the recurrences, initial and salvage therapies and responses observed. It demonstrates the poor outcomes for relapsed disease with only one patient achieving a partial response to second line treatment. Regimens used in the second line setting comprised COP (cyclophosphamide, vincristine and prednisolone), PMitCEBO, VEDex, ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin), VAPEC B (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide and bleomycin) and CHOD/BVAM (cyclophosphamide, doxorubicin, vincristine, dexamethasone, carmustine, cytarabine and methotrexate).

Table IV. Studies of thyroid NHL with 50 or more patients.

Authors/(Refs.)	Year	No. of patients	Sex ratio (F:M)	5-year overall survival (%)
Bitran <i>et al</i> (14)	1977	65	0.81:1	71
Compagno and Oertal (15)	1980	245	2.55:1	53
Anscombe and Wright (16)	1985	76	8.4:1	37
Aozasa <i>et al</i> (17)	1986	79	1.8:1	46
Rosen <i>et al</i> (18)	1988	61	4.1:1	59
Logue <i>et al</i> (3)	1991	70	8:1	42
Matsuzuka <i>et al</i> (19)	1993	119	2:1	100
Tsang and Gospodarowicz (11)	1993	52	Not stated	64
Derringer <i>et al</i> (20)	2000	108	2.7:1	79
Belal <i>et al</i> (21)	2001	52	1.4:1	88
Harrington <i>et al</i> (13)	2005	91	5.5:1	48
Watanabe <i>et al</i> (22)	2011	171	3.9:1	85
Alzouebi <i>et al</i> (current study)	2011	70	4.4:1	60.7

Survival. At the time of writing, 42 patients had died; 26 were alive and in clinical remission and 2 were lost to follow-up. From diagnosis, the median overall survival for all subtypes of NHL was 68 months (range 0-148) or 5.7 years (Fig. 6). Fig. 7 demonstrates overall survival for the different NHL subtypes.

Among the 50 patients with DLBCL, 30 (60%) achieved a complete response, 6% a partial response and 14% had progressive disease despite treatment. In 14%, response was not evaluable due to missing data, loss to follow-up or death due to unrelated causes. The median overall survival was 39 months (3.26 years) with a range of 27-57 months.

Of the 13 MALT lymphomas, 11 (84.6%) achieved a complete response. One patient responded partially and one patient progressed. Three of the six indolent B-cell lymphoma NOS responded completely to treatment whilst in two patients response was only partial.

The single case of T cell lymphoma achieved a complete response with chemotherapy alone. Five-year survival rates for DLBCL, MALT lymphoma and indolent B-cell lymphoma NOS were 45%, 62% and 75%, respectively.

Discussion

Published data on the treatment of thyroid NHL is limited to small numbered retrospective analyses. The authors are unaware of any prospective trials exclusively for thyroid NHL. Table IV demonstrates the studies which have included more than 50 patients. To date, only one UK study analysed more patients than the current study (13).

Overall, the incidence of NHL of the thyroid in this study was 2.1% (i.e. 70 out of 3363) with an average of 1.75 cases diagnosed annually. The patient group is broadly similar to previously described groups in terms of age, gender distribution, stage and pathology. Among our patients 16% had a past history of Hashimoto's disease and 27% had hypothyroidism; a third of these were in patients with MALT lymphoma.

Accurate histological diagnosis was made in the majority of patients with core needle biopsies or resection samples. Two patients were diagnosed by fine needle aspiration and confirmed

as DLBCL. As per previous studies, the majority of primary thyroid lymphomas were of DLBCL and MALT subtypes. We suspect that most of the six cases of indolent B-cell lymphoma NOS would most likely have proved to be MALT lymphomas, as the majority were diagnosed before 1980 when current phenotyping techniques were not available.

Analysis of the data from this series of patients treated over a prolonged period of time in a single centre provides valuable insights into the management of this uncommon condition. It also highlights the significant variation in treatment pathways with some patients managed by surgery, chemotherapy or radiotherapy as a single modality or combination treatment. This experience reflects what was considered to be optimum practice at the time.

This study confirms previous experiences, the preferred method of treatment of localised thyroid lymphoma of indolent subtype is local treatment with either surgery alone and/or local radiotherapy. The dose of radiation administered varies across treating centres and in published series but often a low dose such as 24 Gy in 12 fractions is sufficient. High grade disease is usually best managed with combination chemotherapy or adequate chemotherapy followed by radiotherapy (at relatively higher doses of 30 Gy in 15 fractions as used in current practice) and this is supported by published reports (13,22,23). Nowadays, rituximab would be added to whatever chemotherapy regimen is used (24).

In conclusion, this unselected series of 70 patients treated for thyroid lymphoma demonstrated a response rate of 73% (CR 64%, PR 9%) to treatment and an overall median survival of 68 months. Recurrence was invariably fatal.

References

1. Evans TR, Mansi JL, Bevan DH, *et al*: Primary non-Hodgkin's lymphoma of the thyroid with bone marrow infiltration at presentation. *Clin Oncol* 7: 54-55, 1995.
2. Heimann R, Vannineuse A, De Sloover C, *et al*: Malignant lymphomas and undifferentiated small cell carcinoma of the thyroid: a clinicopathological review in the light of the Kiel classification for malignant lymphomas. *Histopathology* 2: 201-213, 1978.

3. Logue JP, Hale RJ, Stewart AL, *et al*: Primary malignant lymphoma of the thyroid: a clinicopathological analysis. *Int J Radiat Oncol Biol Phys* 22: 929-933, 1992.
4. Freeman C, Berg J and Cutler S: Occurrence and prognosis of extranodal lymphomas. *Cancer* 29: 252-260, 1972.
5. Niitsu N, Okamoto M, Nakamura N, *et al*: Clinicopathologic correlations of stage IE/IIIE primary thyroid diffuse large B cell lymphoma. *Ann Oncol* 18: 1203-1208, 2007.
6. Widder S and Pasiaka JL: Primary thyroid lymphomas. *Curr Treat Options Oncol* 5: 307-313, 2004.
7. Hyjek E and Smith WJ: Primary B cell lymphoma of thyroid and its relationship to Hashimoto's thyroiditis. *Human Pathol* 19: 1315-1326, 1988.
8. Pasiaka JL: Hashimoto's disease and thyroid lymphoma: role of the surgeon. *World J Surg* 24: 966-970, 2000.
9. Graff-Baker A, Sosa JA and Roman SA: Primary thyroid lymphoma: a review of recent developments in diagnosis and histology-driven treatment. *Curr Opin Oncol* 22: 17-22, 2010.
10. Blair TJ and Evans RG: Radiotherapeutic management of primary thyroid lymphoma. *Int J Radiat Oncol Biol Phys* 11: 365-370, 1985.
11. Tsang R and Gospodarowicz M: Non-Hodgkins lymphoma of the thyroid gland: prognostic factors and treatment outcome. *Int J Radiat Oncol Biol Phys* 27: 599-604, 1993.
12. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J and Vardiman JW: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition. IARC, Lyon 2008.
13. Harrington KJ, Michalaki VJ, Vini L, *et al*: Management of non-Hodgkin's lymphoma of the thyroid: the Royal Marsden Hospital experience. *Br J Radiol* 78: 405-410, 2005.
14. Bitran J, Kinzie J, Sweet D, *et al*: Survival of patients with localised histiocytic lymphoma. *Cancer* 39: 342-346, 1977.
15. Compagno J and Oertel J: Malignant lymphoma and other lymphoproliferative disorders of the thyroid gland. *Am J Clin Pathol* 74: 1-11, 1980.
16. Anscombe AM and Wright D: Primary malignant lymphoma of the thyroid- a tumour of mucosa-associated lymphoid tissue: review of seventy-six cases. *Histopathol* 9: 81-97, 1985.
17. Aozasa K, Inoue A, Tajima K, *et al*: Malignant lymphomas of the thyroid gland. *Cancer* 58: 100-104, 1986.
18. Rosen IB, Sutcliffe SB, Gospodarowicz MK, *et al*: The role of surgery in the management of thyroid lymphoma. *Surgery* 104: 1095-1099, 1988.
19. Matsuzuka F, Miyauchi A, Katayama S, *et al*: Clinical aspects of primary thyroid lymphoma: diagnosis and treatment based on our experience of 119 cases. *Thyroid* 3: 93, 1993.
20. Derringer GA, Thompson LD, Frommelt RA, *et al*: Malignant lymphoma of the thyroid gland: A clinicopathologic study of 108 cases. *Am J Surg Pathol* 24: 623-639, 2000.
21. Belal AA, Allam A, Kandil A, *et al*: Primary thyroid lymphoma: a retrospective analysis of prognostic factors and treatment outcome for localized intermediate and high grade lymphoma. *Am J Clin Oncol* 3: 299-305, 2001.
22. Watanabe N, Noh J, Narimatsu H, *et al*: Clinicopathological features of 171 cases of primary thyroid lymphoma: a long-term study involving 24 553 patients with Hashimoto's disease. *Br J Haematol* 153: 236-243, 2011.
23. Pledge S, Bessell EM, Leach IH, *et al*: Non-Hodgkin's lymphoma of the thyroid: a retrospective review of all patients diagnosed in Nottinghamshire from 1973 to 1992. *Clin Oncol* 8: 371-375, 1996.
24. Pfreundschuh M, Trumper L, Osterborg A, *et al*: CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good prognosis diffuse large B-cell lymphoma: a randomised controlled trial by the Mab Thera International Trial (MInT) Group. *Lancet Oncol* 7: 357-359, 2006.